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Craniofacial Region is the Dominant Site in Response to Audio-Visual Contagious Itch in Healthy Humans: An Experimental Study

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Abstract

Introduction: Contagious Itch (CI) is referred to the experience of itch sensation when observing itching or scratching behavior in others or listening to the topic. This phenomenon is observed in humans and animals (monkeys and mice). Cortico-striatal neuronal circuit has been proposed to contribute to CI. Involvement of mirror neurons has also been suggested. We established an experimental audio-visual CI model to explore the impact of body region (craniofacial, arm, back, chest), sex, and sound.

Methods: Twenty healthy young participants were enrolled to watch videos depicting a female or a male demonstrator, presenting itch in 4 body regions with and without sound. Each participant also watched videos of same demonstrators with a neutral content. Itch intensities were rated on a visual analogue scale (VAS 0-10). Three factors of sex, location, and sound were analysed by ANOVA followed by Holm-Sidak post hoc test and P values less than 0.05 were considered significant.

Results: Findings revealed that CI is body region-dependent ($P<0.001$), where craniofacial region was the predominant site compared to arm, chest, and back. Female observers were more sensitive ($P< 0.006$) than males. Male observers were more sensitive to CI than females at the presence of scratching sound ($P=0.04$).

Discussion: Audio-visual itch model was efficient in provoking CI in healthy young adults. Females rated itch intensity higher than males regardless of the body region. Craniofacial region was the most dominant site regardless of sex. Males and females responded differently to sound, where males were more sensitive to audio-visual stimuli.

Introduction

Contagious Itch (CI) is a concept that is referred to the experience of itch sensation when observing itching or scratching behavior in others or even by listening to a discussion related to the topic [1-3]. This phenomenon is not only seen in humans, but also in animals [4]. CI is also relatable to another universal concept, so-called contagious yawning [5]. However, CI has only been subjected to investigation since 2000. Niemeier et al. [1] were the first to reveal that itch can be induced by visual cues. In their study, a group of audiences viewed two presentations of images; the first one was an itch-evoking lecture (images of insects, scratch marks and allergic reactions), whereas the second presentation concentrated on relaxation (pictures of baby skin and children). This study demonstrated a significant increase in scratching when observing the "itch lecture" in comparison to the "relaxation lecture"[1]. Several years later, another study [6] approached an almost identical procedure, aiming to investigate if visual stimuli without auditory cues would evoke itch. They asked groups of students to watch video clips to provoke coldness, pain, or itch. The itch-evoking video depicted images of head lice moving and people scratching their heads. This itch-evoking video led to more scratching and higher levels of itch compared to the videos depicting coldness and pain [6]. Two years later, another study [3] applied visual stimulus to induce itch. This group presented a video of a person scratching himself to a control group and a group of Atopic Dermatitis (AD) patients. Both groups showed an increased scratching behavior by watching the experimental video compared to the control video with the neutral content [3]. However, the AD group rated a significantly higher itch intensity compared to the control group. This indicates that AD patients are more susceptible to itch-inducing audio-visual stimuli in contrast to healthy controls [7]. Another study in 2013 [8] investigated if visual cue could provoke itching and scratching response in healthy females using different images. The participant were presented two different Power Points, an itch related (e.g. ants, fleas or skin conditions) and a neutral one (e.g. butterflies or healthy skin).The presentation slides were moreover divided into types such as 'skin contact' (e.g. ants crawling on the hand or a butterfly on a finger), 'skin response' (e.g. scratching an insect bite or washing the hands) or 'context only' (e.g. viewing midges or birds flying). The study showed an increased itch intensity when viewing the itch related presentation compared to the neural presentation [8].

Besides human studies, animal studies of CI have also been conducted. For instance, a group of researchers [4] demonstrated CI in monkeys who observed itching and scratching behavior of other monkeys represented in videos. A recent study in non-mammals (mice) also presented similar results, where mice presented scratching behavior after noticing scratching animals in an adjacent cage [9-11]. This finding indicates that not only humans are prone to CI, but also non-human primates and non-mammals' mice can present CI behavior [9-11].

The neural mechanism of CI has been examined by two prior fMRI studies [12,13] proving activity in several brain regions, such as Insular Cortex (IC), Supplementary Motor Area (SMA), Premotor Cortex (PM), and Prefrontal Cortex (PFC) during observation of other individuals sensing itch. Investigating the role of empathy in pain, similar brain regions have been found activated [14,15]. Anterior Insular Cortex (aIC) is associated with empathy for itch. Another group [13] set up an experiment, analysing brain activity of subjects imaging the itch sensation while watching images of itching skin and at the same time images of painful skin. They wanted to further test the empathy and role of aIC. Identical activation processes were observed; however, there was a difference in functional connectivity between itch and pain in brain images. Additionally, there was a significant increase in functional connectivity between the aIC and basal ganglia during the itch sensation. The basal ganglia is composed of an anatomical circuit including areas such as the SMA, PM, and MI. This circuit functions in motor control. The aIC is anatomically related to the basal ganglia [16] and if any lesions appear in the aIC, motivation and craving in general are inhibited [17]. Hence, a potential process behind the scratching reaction that occurs when observing others could be that activation of aIC that motivates directly or indirectly motor activity in the cortico-striatal circuit via the basal ganglia leading to scratching response. Another possible mechanism underlying CI could potentially be functional coupling between aIC and global pallidus (GP) [13]. GP has the function of encouraging acts and "goal-directed behavior" [18,19]. This finding could propose that dissimilarity in the functional coupling may explain the reason behind increased motor response, while observing itch in others. A former fMRI study in CI has demonstrated that during itch stimuli (viewing others itching and scratching), SI was significantly activated [12] whereas this region in pain studies is found to associated with empathy for pain. Two additional brain imaging studies focused on somatic hallucination and found a significant activation of the medial parietal cortex along with the posterior cingulate cortex and precuneus [20,21]. Precuneus plays an important role in memory [22]; hence, the memory of experiencing itch may potentially contribute to the underlying mechanism of itch transmission while viewing others' itch experience or scratching. Moreover, there is a non-mammal study [10] that has looked deeper into the underlying mechanisms of CI. This study demonstrated, by molecular mapping, a greater neural activation in the Suprachiasmatic Nucleus (SCN) of the observer mice experiencing scratching sensation when observing another mice scratching. The study concluded that depletion of gastrin-releasing peptide (GRP) receptor (GRPR) or GRPR neurons in SCN inhibits contagious scratching behavior whereas excitation of GRP/GRPR neurons could improve scratching behavior, proposing that GRP-GRPR signalling is an important pathway in CI [10].

The underlying mechanism of CI is not completely understood; hence, different hypotheses have been made; one of which is the activation of Mirror Neurons (MNs). MNs are a specific group of neurons that are activated when performing a motor act and imitating others executing a similar motor act. MNs have become more and more popular due to its contribution to elucidation of social behavior, imitation, language processing and other parameters like empathy, emotion recognition and intention-reading, etc. No association has yet been established between CI in human and MNs; however, one study [4] has reported that CI is a common phenomenon in primates. This could indicate that MNs may also play a role in CI in humans. By reviewing the experiments where abstract stimuli have been approached to induce itch, it can be speculated that itch sensation that is occurred due to itch depicting images, may be involved in activating the sensory-emotional elements of the MNs. The elements of MNs include Anterior Cingulate Cortex (ACC) and the Anterior Insula, and these brain regions are commonly found in studies related to pain empathy [23]. Such findings emphasize that pain and itch are not only physiologically closely related but that psychology of pain and itch also overlaps in some aspects [24].

CI is still a less studied area and there are still number of open questions in the field that require further investigation. Hence, we established an experimental CI model to explore the impact of sex and body region on CI. We compared responses of craniofacial region to other body regions such as arm, back, and chest in females and males. We also investigated if any significant difference exists in itch intensity when observers are exposed to visual itch stimuli with and without scratching sound. We hypothesized that participants would be more susceptible to CI within craniofacial region compared with arm, chest, and back. We also proposed that visual cues with sound would have a higher impact reflected on higher itch intensity rated by the participants. As females tend to show more empathy [25] than men, we also hypothesized that a sex-related response would be detectable with females being more prone to visual itch stimuli.

Methods

Participants

A group of 20 healthy participants (10 females and 10 males), 18-34 years (26.15±4.66 years (Mean±SD)) were recruited. Exclusion criteria included 1) any previous or skin-related conditions 2) allergic disorders 3) any ongoing itch 4) rashes or lesions on the particular body regions and 5) any pain or discomfort at the day of the experiment. All participants signed a written informed consent before participating in the experiment in accordance with the 2013 version of the Helsinki Declaration [26]. The study protocol was communicated with the regional ethics committee of the Northern region in Denmark for obtaining ethical approval, but it was confirmed that there was no necessity for an approval on conduction of this study due to the nature of this study.

A randomized controlled cross-over study was designed. The study consisted of three steps. First step included a questionnaire, which had to be filled out before the experiment. Second step was presentation of the two Experimental Videos (EV), both with and without sound presented in a randomized order based on sex and sound to avoid a potential bias. Fifteen minutes of washout period between each video presentation was established to avoid a carry-over effect. Third step consisted of the two Control Videos (CV) presentation composed of a neutral content, where the same demonstrators were recorded but in a relaxed and idle condition. The participants were seated in a quiet room without any distractions, and the videos were presented on a computer and when the videos with sound were presented, headphones were provided. Participants were instructed to rate itch intensity on a visual analogue scale (VAS 0-10) after each video and to draw the itching areas on the body chart (Figure 1).

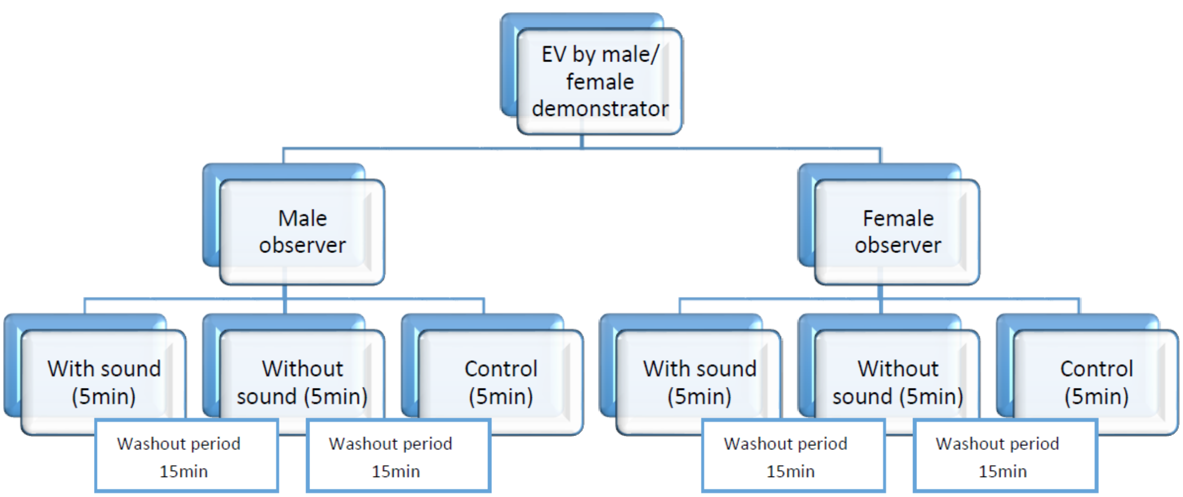

Figure 1: Experimental setup. Each participant has been exposed to two EVs with a male and a female demonstrator, respectively. Both EVs were presented with and without sound with a washout period of 15 minutes in between, and a presentation of control video. EV: Experimental video. Please note that the order of the tests was randomized.

Questionnaire

The questionnaire was composed of questions based on demographic variables, such as sex, age and personality traits including extroversion, neuroticism, openness to experiences, agreeableness and consciousness, which was based on the so-called Five Factor Model (FFM) [27]. Additional questions were asked about whether the participants received any medications, and how they would describe their mood at the time of experiment.

Videos

Four videos were recorded by the investigators capturing demonstrators either scratching themselves or sitting relaxed.

Each video was of 5 minutes length. Two of the videos displayed a female demonstrator while the other two videos displayed a male demonstrator. The demonstrators were instructed to itch and scratch specific areas, arm, chest, back and craniofacial region. Two videos (female-male) were dedicated to controls and two (female-male) to the scratching behavior. The EV depicted either a female or male demonstrator itching and scratching, whereas the CV depicted the same demonstrators, but in a relaxed and idle condition.

Body Charts

Body charts were used to mark on 4 target sites of arm, chest, back and craniofacial region for itching sensation following exposure to the videos.

Rating of Itch

A VAS scale anchored with 0 and 10 (0=no itch, 10=extreme itch) was provided in order to rate the intensity of itch.

Statistical Analysis

Data were analysed by Sigma Plot 14.0. A normality test was performed using the Shapiro-Wilk test. P-values ≤ 0.05 were considered as significant. A three-way analysis of variance (ANOVA) was applied to compare itch intensity on VAS based on 3 factors: sex (with two levels; male and female), location (with four levels; craniofacial region, chest, arm and back) and sound (with two levels; with and without sound). If ANOVA results showed a significant difference, *post-hoc* test, Holm-Sidak, was applied to identify where the exact difference was located. Data are presented as means and standard deviation, standard error of the mean, or percentages in text and figures, unless otherwise stated.

Results

All enrolled participants completed the experiments. Out of 20 participants, 4 reported some itchiness while watching the CV with and without sound. These 4 participants did not show a variation in rating response.

Data analysis revealed that CI could be induced in healthy participants. A main effect of sex was found (ANOVA, $F(1,288)=7.691$, $P< 0.006$) where females were more sensitive than males (Figure 2). There was also a significant main effect of location (ANOVA, $F(3,288)=8.706$, $p<0.001$), indicating that body regions show different susceptibility to perception of CI (Figure 2). Holm-Sidak post hoc yielded a statistically significant interaction between females and the craniofacial region ($P<0.001$), suggesting that among the four regions, craniofacial region was most sensitive to CI in females (Figure 2). However, this was not the case for males. Within the craniofacial region, a statistically significant difference ($P=0.04$) was also observed between male and female observers, indicating that itch intensity was more pronounced in the craniofacial region in females (Figure 2). However, no significant main effect of sound was yielded, (ANOVA, $F(3,288)=0.779$, $p < 0.507$), indicating that sound overall did not influence the itch sensation under conditions of this experiment.

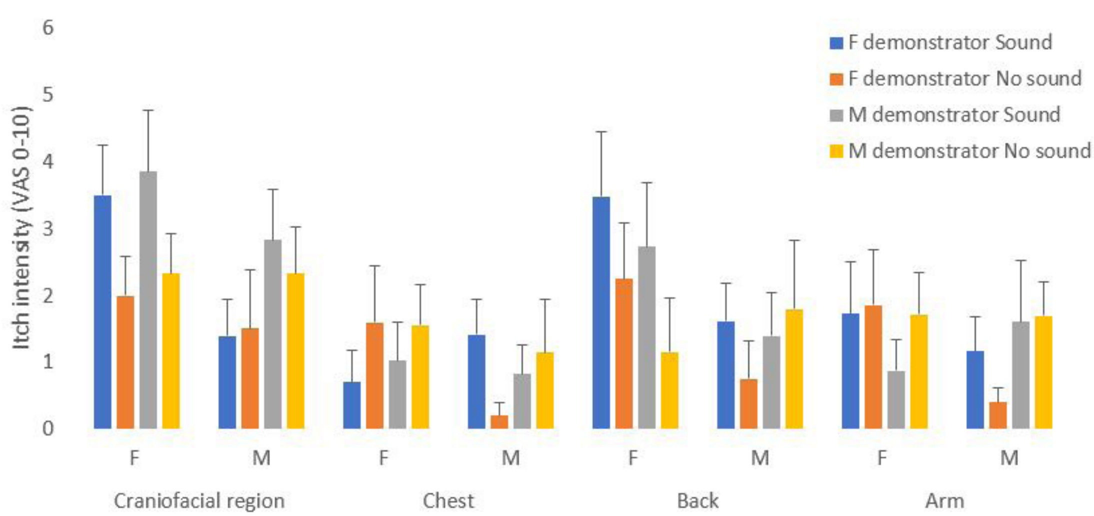

Figure 2: Illustration of the effect of audio-visual-evoked itch in healthy male and female participants rating itch intensity on VAS (0-10) and the effect of audio-visual-induced itch on the specific body regions, including craniofacial region, chest, back and arm. F: Female, M: Male. Data are presented as Mean±SEM (Standard Error of the Mean).

Looking into interactions of the sound results, it was evident that for females, videos of a female demonstrator without sound, was significantly different from males (p=0.04), which indicates that female observers were more sensitive to CI without sound compared to male observers.

Moreover, there was a statistically significant difference within the craniofacial region vs chest region (P=<0.001) and craniofacial vs arm (P=0.004) when EV depicting male demonstrator was presented with sound. This indicates that the craniofacial region was more prone to CI than chest and arm, but still with an influence of sex.

Discussion

The purpose of the present study was to further investigate the phenomenon of CI and that whether audio-visual stimuli had any additional impact on healthy participants in particular in relation to body regions. Additional factors, such as sex and sound were also examined. Overall, the results from this exploratory study confirm that audio-visual stimuli depicting itch-related scenarios can evoke itch in healthy adult individuals, the phenomenon is sex-related, and the craniofacial region is more sensitive. Below, the findings are discussed in more details.

Sex

The current study showed that females exhibit more sensitivity to itch by rating higher scores on VAS compared to males when exposed to the audio-visual stimulation. Female also expressed higher itch intensity in the craniofacial region compared to males. Based on a former study [25], it has been proposed that females express higher empathy, which makes them better at relating and empathizing with the internal emotional conditions of others; hence, this might be an explanation as why females are more responsive to visual itch stimulation. One possible mechanism underlying this empathic process is the MNs [28], which is arguably an inherent mechanism that captures actions of the surroundings. This idea [3] states that contribution of MNs might be a built-in mechanism, since CI occurs following to visual cue, in healthy individuals and in AD patients, though in lower magnitude, comparatively. This indicates that activation of MNs may be amplified in AD patients during visual itch stimuli [3]. According to Ferrari et al. [29] MNs have immense control over facial motor acts (biting, sucking); hence, MNs may also contribute in CI [18,30,31]. Alternative possibilities behind the difference in itch response between the sexes could be due to difference in thresholds scratching. This means that some people feel itchy, but their motor action of scratching comes later than others.

Location

The present study also showed that the craniofacial region was mostly affected by the audio-visual stimuli. Based on the previous studies, it has been reported that body parts that response to itch visual cue vary between chronic itch patients and healthy controls. A study from 2011 [3] reported that AD patients scratched body regions distal from the body parts that were scratched in the videos; while the healthy control scratched body parts, proximal to the body regions that were scratched in the presented video. This evidence is supported by another study [32], where healthy participants in their study showed an increased itch perception at proximal body site (head), despite viewing scratching of the chest and arm. Interestingly, macaque monkeys [4] exhibit almost identical scratching behavior as humans, when exposed to video presentations of other monkey executing scratching behavior. Taken together, these findings indicate that CI is not linked to one specific body location, but some locations might be more sensitive than others. Further investigation is required to substantiate our findings of CI in the craniofacial region.

Sound Effect

This study investigated whether itch perception would be affected by audio stimuli and the results showed that the audio parameter overall does not have any impact on itch perception in participants. Therefore, visual stimuli can be considered the main drive for CI. However, the itch sensation was evidently more increased in the craniofacial region comparatively to the chest and arm, while observing the EV with the male demonstrator presented with sound. Therefore, effect of sound might be sex-dependent and also region-dependent. This needs further investigation. Similar results have been reported in a previous study [33], where the authors concluded that audio increased itch susceptibility both in the psoriasis and healthy group without peripheral stimulation (e.g. ants crawling or insects bites). A potential explanation on why sound could have an additional effect to the visual cue is that a potential mechanism where the motor execution of scratching and connected somatosensory sensations of certain body parts are simulated/imitated in the observers' brain, which triggers the auditory MNs [33]. The MNs contains the so-called area F5, which is composed of audio-visual MNs. These neurons are fired not only when observing a movement execution but also when only the sound of the same movement is captured [34]. This potential function of MNs suggests an audio-visual motor association between visualization, motor act, and sound [35]. This might also explain the results of the present study, indicating that this area might have been activated during the EV with the sound of scratching and visualizing of itch at the same location.

Higher cortical regions might also be involved in the overall response. For instance, unpleasantness of itch sensation, which is an affective aspect of itch, may share similar region in the brain, insula, for reaction. Overall response in CI is not a simple result of motor act and body region but a higher cortical response. Therefore, currently we could only present that female and males responded differently to sound, but the mechanism underlying such effect is not clear to explain. Since females- by nature - are more empathetic in general they might have related more to the demonstrators in the EV even without sound compared to males [25,36].

Study Limitations and Future Perspectives

For the analysis, only the sex of the observers was taken into consideration, and the sex of the demonstrator was considered only in combination with the videos, either with or without sound. Since it has been shown that in pain, both the sex of subjects, and investigators can influence the outcome of pain intensity [37], future studies with larger population could also test this hypothesis for CI. This would be in particular interesting as in clinic sex related differences in itch have been shown [38] and human experimental models of itch have also demonstrated sex-related differences in response to evoked itch [39].

It is important to emphasize that besides sex, locations, and sound, personality trait is another potential factor that can conceptualize one's susceptibility to audio-visual itch stimuli. Former studies [12,40,41] have proposed that among healthy young adults, neuroticism is the most common personality characteristic and that can affect responsiveness to sensory stimuli. Additional factors that have been linked with increased itch intensities, involve negative emotions such as anxiety. One study [6] has found a correlation between itch and anxiety. In this study, the students who felt itchiness also expressed anxiety, which may indicate that people with a certain mood can be affected by itch differently. Another example is the study by van Laarhoven et al. [42], who reported that females in positive emotional condition experienced reduced itch intensity compared to those with negative emotions. It is noteworthy to mention that there are several other studies that have been able to reveal strong correlations between personality traits and itch perception in healthy and patients with skin-related conditions [7]. Even though these results propose a correlation between negative emotions and personality traits and an increase in itch intensities, personality trait should only be treated as a factor that can exacerbate the experience of itch and not as a potential cause of developing itchy skin-disorder [7]. Due to the relatively small sample size, we could not manage to establish the impact of personality trait on CI. The personality traits of the female participants were as follows 30% expressed extroversion, 20% consciousness, 20% agreeableness, 20% openness and 10% neuroticism. Male participants were presented as 70% extroversion, 20% consciousness and 10% agreeableness.

The expletory nature of this study in addition to a relatively small sample size, did not allow us to establish the impact of age on CI. Age might be an influencing factor in responsiveness to CI. Additionally, it is not known whether there is any difference in susceptibility to CI depending on race, and hence a heterogeneous group should be approached in future studies. We did not account for the time of cycle in females. Impact of hormones on CI could be taken into considerations with a potential of fluctuation hormonal pattern during menstrual cycle on CI responsiveness in females.

Conclusion

Our study confirmed that audio-visual itch model was efficient in provoking CI in healthy young adults. Females rated itch intensity higher than males regardless of the body region. Craniofacial region was the most dominant site regardless of sex. Males and females responded differently to sound, where males were more sensitive to audio-visual stimuli.

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